PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB2004/001619	14.04.2004	17.04.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/12, A61K39/40, C12Q1/68, G01N33/563

Applicant
NEUTEC PHARMA PLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/GB2004/001619

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19 (with respect to IA); 30 (partially)

because:

☒ the said international application, or the said claims Nos. 19 (with respect to IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-3,30 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

2.1 The subject-matter of claim 2 lacks novelty over D1 (Fig. 2, claim 8, SEQ ID No. 15) and D2 (Fig. 1b, claim 14, SEQ ID No. 37 and 50) as they disclose CDR-L3 sequences according to present SEQ ID No. 33 (Art. 33(2) PCT).

2.2 The subject-matter of claims 1 and 3-30 is novel over the prior art which does not disclose the combination of features suggested by the said claims (Art. 33(2) PCT).

3.1 Claim 1 aims at providing CDR-H3 sequences that are associated with C. difficile infection or vaccination. However, the sequences according to SEQ ID Nos. 27, 28, 30 and 31 were shown to exceed the frequency threshold level of 1% only in two C. difficile infected patients. The sequence according to SEQ ID No. 29 was only identified in a single C. difficile infected patient and is moreover associated with septicaemia with methicilin-resistant S. aureus as further evidenced by the post-published document D4. Hence, there is no sufficient experimental support to assume that the CDR-H3 sequences according to claim 1 are indeed associated with C. difficile infection or vaccination. Consequently, the problem underlying claim 1 has to be formulated in more generic terms, namely as the provision of further CDR-H3 sequences. Provision of CDR-H3 sequences involves nothing but routine experimentation (cf. e.g. D1-D3), and hence no inventive step can be acknowledged for the subject-matter of claim 1 (Art. 33(3) PCT).

3.2 For similar consideration also the subject-matter of claim 3 is considered to lack an inventive step (Art. 33(3) PCT).

3.3 D3 discloses primers used in a method of amplifying CDR3 sequences by PCR. The subject-matter of claim 30 is distinguished from D3 representing the closest prior art in that the primers are incorporated into a kit. However, the incorporation of known primers into a kit, thereby providing the less skilled with the reagents for performing a known method using said primers, is a matter of common practice and does not establish an inventive step (Art. 33(3) PCT).

3.4 Claims 17 and 19 aim at providing a medicament for the treatment of C. difficile infections (claim 17) as well as a method of treating the said infections (claim 19). The solution is based on the provision of an antibody specific for C. difficile, respectively the use thereof. The application, however only teaches CDR3

sequences of antibodies associated with the said infection. The application discloses neither antibodies having the said specificity nor sufficient information as to how these antibodies can be synthesised (cf. 5.1 - 5.3 herein below). Therefore, the foregoing problem cannot be considered as being solved and consequently no inventive step can be acknowledged for the subject-matter of claims 17 and 19 (Art. 33(3) PCT).

3.5 The same applies to dependent claim 18 (Art. 33(3) PCT).

3.6 Claim 4 solves the problem of identifying candidate sequences of at least the CDR3 region of antibodies specific against at least one antigen produced by C. difficile during infection or against a vaccine. The solution involves determining in B cells CDR3 sequences that have a frequency of more than 1%. None of the prior art documents, neither alone nor taken in combination, fairly suggests the subject-matter of claim 4 which is therefore considered to involve an inventive step (Art. 33(3) PCT).

3.7 The subject-matter of claims 22, 28 and 29 refer to different applications of determining the frequency of CDR3 sequences in B-cells of individuals/patients for the solution of different problems, namely of determining the efficacy of a vaccine (claim 22), of detecting a C. difficile infection (claim 28), or of determining the susceptibility of a patient to a C. difficile infection (claim 29). Thus, similar considerations as under 3.4 also apply to the said claims (Art. 33(3) PCT).

3.8 For the foregoing considerations (cf. 3.6 and 3.7) claims 20, 21, 26 and 27 which incorporate the said inventive methods of claim 4 (claims 20 and 21) and claim 22 (claims 26 and 27) are also considered inventive (Art. 33(3) PCT).

3.9 The same considerations as under 3.6 - 3.8 also apply to the dependent claims 5-16 and 23-25 (Art. 33(3) PCT.

4.1 For the assessment of the present claim 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such

a compound for the manufacture of a medicament for a new medical treatment.

4.2 Industrial applicability for the subject-matter of claims 1-18 and 20-30 is acknowledged (Art. 33(4) PCT).

5.1 Claim 17 is formulated as a "reach through claim". The claim in fact refers to a two step process, wherein the first step comprises a method of screening and the second step a method of production. However, as the input into the production step is to be determined by the screening step it cannot be determined, and thus the product obtained by the whole method is not defined thereby leaving the scope of claim 17 unclear (Art. 6 PCT).

5.2 Moreover, the description only supports the identification of CDR3 sequences of either heavy or light chains that are associated with C. difficile infections or with vaccination thereagainst. No support is provided for the synthesis of an antibody specific for C. difficile on the basis of said CDR3 sequences (Art. 6 PCT). Even more so, for an antibody to be specific for C. difficile i.e. that may be used as a medicament for the treatment of C. difficile infections, at least whole V_H or V_L domains comprising all three CDRs of either domain have to be synthesised (cf. D5). Thus, the feature of the invention covered by claim 17 is not considered to be disclosed in a way sufficiently clear and complete for it to be carried out by the skilled person (Art. 5 PCT).

5.3 The same considerations as under 5.1 with respect to clarity (Art. 6 PCT) as well as under 5.2 with respect to support (Art. 6 PCT) and sufficiency of disclosure (Art. 5 PCT) also apply to claim 19 as well as to dependent claim 18.

6. Should the priority of the present application not be valid, the D4 would be relevant with respect to novelty and inventive step (Art. 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the above document could be relevant to the question of novelty.